

Detailed Protocol for a Study Entitled

# Effect of IV Vitamin C, Thiamine, and Steroids on mortality of Septic Shock

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## I BACKGROUND AND SIGNIFICANCE

Septic shock is a life-threatening condition that is characterized by a collapse in the ability of the organism to maintain adequate blood pressure and end-organ perfusion secondary to sepsis—a dysregulated inflammatory response triggered by an infection.<sup>1</sup> It is highly prevalent in the intensive care unit (ICU) and carries a high morbidity, mortality and socioeconomic burden around the world. Sepsis accounted for more than \$23 billion (6.2%) of total US hospital costs in 2013.<sup>2</sup> Many resources have been expended in an effort to decrease the mortality of sepsis and septic shock via a plurality of public campaigns, initiatives, government mandates, and hospital protocols. The cornerstones of treatment largely consists of early identification of sepsis, infectious source control, early antibiotics and supportive therapy with intravenous fluids and vasopressors.<sup>3</sup> Attempts to identify effective therapies targeting the inflammatory mechanisms of sepsis have largely been ineffective.<sup>4</sup>

Recently, a study conducted by Marik et al demonstrated a remarkable decrease in the mortality of septic patients who received a multi-drug “cocktail” of intravenous vitamin C, hydrocortisone, and thiamine.<sup>5</sup> The cocktail has been developed based upon emerging clinical and experimental evidence demonstrating the effectiveness of these medications in mitigating the underlying pathological and physiological derangements that characterize sepsis.<sup>6</sup> The study reported by Marik et al was, unblinded, and without concurrent controls. As a result, the validity of the study has been called into question due to the lack of methodological rigor necessary to support a cause and effect relationship between the treatment regimen and the dramatic decrease in mortality.

Our goal is to evaluate the effectiveness of intravenous vitamin C and thiamine in patients with septic shock being treated with corticosteroids using a double-blind, prospective, randomized controlled trial. If the therapy is as effective as demonstrated in the initial study, a marked reduction in sepsis mortality will be achieved with little cost and risk.

## II. SPECIFIC AIMS

The primary objective of this study is to prospectively determine the effect on hospital mortality of the addition of intravenous vitamin C and thiamine to the treatment regimen of critically ill patients with septic shock admitted to the ICU of an urban community hospital.

Our secondary aim is to evaluate the effect of the therapy on multiple other clinical parameters including but not limited to hospital length of stay, ICU length of stay, 30-day mortality, 60-day mortality, incidence and duration of delirium, need for vasopressor support, need for renal replacement therapy, change in SOFA scores, etc.

## III. SUBJECT SELECTION

### Inclusion criteria:

Patients admitted to medical intensive care unit (MICU) for less than 24 hours, who are hypotensive despite a fluid bolus of 30 mL/kg and who are requiring pressors to keep MAP > 65 of at least 5 mcg/min of levophed or equivalent and whose shock is clinically suspected to be secondary to sepsis.

Vasopressor equivalency will be determined based on the following conversions to  
 1.0 norepinephrine( $\mu\text{g}/\text{min}$ )  
 = epinephrine ( $\mu\text{g}/\text{min}$ )  
 = dopamine( $\mu\text{g}/\text{kg}/\text{min}$ )  $\div$  2  
 = phenylephrine ( $\mu\text{g}/\text{min}$ )  $\div$  10  
 = vasopressin (units/h)  $\times$  8.33

These conversions are adapted from the VASST trial.<sup>7</sup>

In addition, stress dose corticosteroids, hydrocortisone 50mg IV Q6hrs, will have to have been started or intended to be started.

#### **Exclusion criteria:**

- Contraindication to corticosteroids, thiamine, or vitamin C
- Treating physician opposed to administering corticosteroids to the patient
- Age < 18 years
- Pregnancy
- DNR/DNI/limitations of care
- Patients with a fatal underlying disease who are unlikely to survive to hospital discharge
- Patients with a primary admitting diagnosis of an acute cerebral vascular event, acute coronary syndrome, active gastrointestinal bleeding, burn or trauma
- Requirement for immediate surgery
- Patients with HIV and a CD4 < 50 mm<sup>2</sup>
- Patients with known glucose-6 phosphate dehydrogenase (G-6PD) deficiency.<sup>8</sup>
- Involvement in another clinical trial

#### **Source of subjects and recruitment methods:**

This study will be conducted in the MICU at NYP Brooklyn Methodist Hospital. Source of subjects includes all private and service patients admitted to the MICU. Prior to admission, as a routine procedure, all patients are first evaluated by an on-call critical care fellow who, alongside a critical care attending, determines whether admission to the MICU is warranted. The screening for inclusion into this study will thus be performed by the fellows during this evaluation. If the patient fits the inclusion and exclusion criteria, the fellow will log the MRN into the record (see appendix) and the patient will then be approached for consent by either the research associate, the fellow, or another physician.

### **IV. SUBJECT ENROLLMENT**

Once screened for inclusion, consent will be obtained by a trained person familiar with the protocol and consent process of this study. The trained person will most likely be a research associate; however, if unavailable, consent process may be performed by the physician taking care of the patient, ICU fellow, or another person directly involved in the study. Consent will be obtained directly from the patient if the patient has capacity to make their own healthcare decisions. If the patient does not have capacity, consent will be obtained from the healthcare proxy(HCP), and if no healthcare proxy is available, consent will be obtained from the next-of-kin. Consent may be obtained over the phone if no one is available at the bedside to provide the consent, however written consent should be obtained as soon as possible.

Once consent is obtained, the subject will be enrolled in the study and the fellow will be notified to place study protocol orders. Once orders are placed, the pharmacist will then randomize the patient and compound the appropriate medications (i.e. placebo vs interventional).

### **V. STUDY PROCEDURES**

#### **Vitamin C, Hydrocortisone and Thiamine dosing protocol and randomization**

This is a double-blind randomized placebo controlled study. Only the dispensing pharmacist, who has no clinical interaction with the patient and is not part of the bedside treatment team, will be aware of the treatment allocation. Patients will be randomized into one of 2 groups: the intervention group and the control group. Intervention group will receive intravenous vitamin C and thiamine according to the dosing regimen described below. The control group will receive placebo that is prepared to look identical to the medications within the intervention group.

Randomization will be performed using a random number table generated by the dispensing pharmacist using randomization software. The software will generate subject IDs from 1 to 130 and randomize half of the IDs to the control and half to the treatment group. The table will be generated prior to enrollment of the first participant. Once enrollment begins, each participant's medical record number (MRN) will be assigned to the subject IDs in sequential order from 1 to 130. This process will be triggered by the fellow ordering the vitamin C protocol. Only the pharmacist will have access to the table(which will be stored securely) until completion of the study.

The hydrocortisone, vitamin C, thiamine, and their corresponding placebos will be formulated as follows:

**Vitamin C:** Vitamin C is provided by the manufacturer as a 50 ml vial at a concentration of 500mg/ml. Three (3) ml of vitamin C will be placed in a 50 ml bag of Normal Saline (1500mg vitamin C in 50ml bag) which will then be infused over 1 hour. The bag will be labeled by the pharmacy as Vitamin C. The dosing schedule is 1500mg every 6 hours for 4 days or until discharge from the ICU.

**Vitamin C placebo** will consist of an identical bag of 50cc normal saline (but with no vitamin C) and will be labelled vitamin C. Placebo will be infused over 30-60 minutes as per the infusion instructions of the active vitamin.

**Thiamine:** As a high percentage of septic patients have been shown to be thiamine deficient, patients will receive intravenous thiamine 200mg q 12 hourly for 4 days or until ICU discharge. Thiamine is also a cofactor for the metabolism of oxalate (a byproduct of vitamin C metabolism), with thiamine deficiency increasing oxalate levels. Thiamine placebo will consist of 50mL of 5% dextrose.

**Steroids:** Hydrocortisone 50 mg IV q 6 hourly will be continued for at least 4 days or until ICU discharge. All patients(both in the treatment and the control groups) included in the study will receive this steroid regimen. If participants were already started on steroids for another indication (i.e Asthma) prior to inclusion, they may continue their regimen as long as the dosing is equivalent to the steroid regimen described above. Alternatively, dosing may need to be increased or regimen switched entirely to the one described in this protocol. This decision will be made by the treating physician.

Procalcitonin will be drawn at time of admission and again at 96 hours after admission.

Patients who are enrolled in the study will have their capillary blood glucose levels measured using the StatStrip Glucometer and Test Strips. This glucometer is currently being used for all patients at NYPBMH.

**Data collection:** data collection will be performed by the research associate and other study personnel in real time and as the schedule allows. The data collection sheet (see Appendix) will include all needed data associated with the patient's MRN. Once the data sheet is completed, the patient's treatment group can be unmasked – this will occur after the 60 day mark, as that is the last datapoint (60-day mortality).

## VI. STATISTICAL ANALYSIS

### **Primary Outcome**

- Hospital mortality

### **Secondary Outcome**

- ICU mortality
- 30-day mortality
- 60-day mortality
- Time to vasopressor independence. Defined as the time from starting the active treatment/placebo to discontinuation of all pressors
- PCT clearance (PCT-c) calculated using the following formula: initial PCT minus PCT at 96 hours, divided by the initial PCT multiplied by 100.
- Delta SOFA score, defined as the initial SOFA score minus the day 4 SOFA score
- ICU length of stay (LOS) and ICU free days. ICU free days is calculated as the number of days alive and out of the ICU to day 28
- Hospital LOS
- Incidence of delirium and duration of delirium
- Incidence of AKI
- Effect of sex on outcome

**Power Analysis:**

The published hospital mortality for patients with severe sepsis and septic shock in the USA approximates 40%. Based on the previous study by Marik et al we project that the addition of vitamin C and thiamine could reduce the mortality to 15%. Assuming a type 1 error of 5% (alpha of 0.05) and a power of 90% (the ability to detect a difference between two groups when a difference exists) would require a sample size of 65 patients in each group. We expect the control group and the intervention group to be equal due to random assignment, thus we will require at least 130 participants.

**Data Collection:**

The following deidentified demographic and clinical data will be collected:

- Age (18-90); patients over age 90 will be recorded as 90 years
- Sex
- Weight
- Admitting diagnosis and site of infection
- Culture results
- Co-morbid conditions
- Charlson co-morbidity index
- Requirement for mechanical ventilation (Y/N).
- Duration of mechanical ventilation
- The hourly dosage of vasopressors will be recorded as the norepinephrine equivalent dosage.
- Duration of vasopressor use
- Time to vasopressor independence from start of active drug/placebo
- Daily urine output (for first 4 days)
- Net Fluid balance after 24 and 72 hours
- Presence of acute kidney injury (AKI). Presence of AKI: Acute kidney injury (AKI) will be defined using the KDIGO criteria; namely, an increase of the s-creatinine  $> 0.3$  mg/dl or a level  $> 1.5$  times the baseline value. If the baseline s-creatinine is not known a value  $> 1.5$  mg/dl will be regarded as diagnostic of AKI.
- Time from hospital admission to first dose of vitamin C
- Time from ICU admission to first dose of vitamin C
- Length of ICU and hospital stay
- ICU, hospital, 28-day and 60-day survival
- Routine laboratory data for 4 days including:
  - a. basic metabolic profile
  - b. complete blood count
  - c. total bilirubin
  - d. PaO<sub>2</sub>/FiO<sub>2</sub> ratio
  - e. Procalcitonin (PCT)
  - f. lactate level
- The patients' admission APACHE II scores will be recorded.
- The patient's vital signs especially as necessary for calculation of a daily SOFA score for 4 days or until ICU discharge, whichever happens first.
- Glasgow Coma Scale (as necessary for calculation of SOFA and APACHE scores)
- The daily SOFA (Sepsis-related Organ Failure Assessment) score will be recorded for the first 4 treatment days.
- ICAM +ve Delirium (y/n) and days with delirium

**VII RISKS & DISCOMFORTS (Stratify by common and uncommon)**

- Ascorbic acid has been associated with development of acute or chronic oxalate nephropathy following prolonged use of high doses of ascorbic acid infusion. Patients with renal disease including renal impairment, history of oxalate kidney stones, geriatric patients, and pediatric patients less than 2 years old may be at increased risk.<sup>9,10</sup>

- Patients with glucose-6-phosphate dehydrogenase deficiency are at risk of severe hemolysis; a reduced dose is recommended.<sup>8</sup>
- Ascorbic acid may interfere with laboratory tests based on oxidation-reduction reactions, including blood and urine glucose testing. (Medication package insert)
- Ascorbic acid may decrease the activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid. (Medication package insert)
- Ascorbic acid may cause acidification of the urine and result in decreased amphetamine serum levels and affect excretion and plasma concentrations of other drugs sensitive to urine pH. (Medication package insert)

## VIII. BENEFITS & RISKS

### **Benefits and/or risks to participants**

The participants selected for this study will be patients who are critically ill and have a high risk of death as a consequence of their critical illness (septic shock) that is part of the inclusion criteria. The benefit of participating in this study includes being treated with a potentially highly effective treatment that may markedly increase their chances of survival, as well as improvement in end-organ function including renal function, decreased risk of needing dialysis, improvement in mentation and cognition and others.

The risk to participants can potentially include the side effects from using intravenous vitamin C and vitamin B1. One such cited risk is potential kidney injury in the form of oxalate nephropathy that has been observed in patients with chronic renal failure receiving high dose vitamin C.

### **Benefits and/or risks to society (e.g., increased understanding of disease process, etc.)**

Given the substantial socioeconomic, as well as morbidity and mortality burden of sepsis on the population of the world, the potential benefits to society are great. Our goal is to investigate a therapy that, if proven to be beneficial, will identify a highly effective treatment that is inexpensive and readily available. This treatment will be available not only to patients in affluent countries, but affordable around the world as well. Furthermore, this treatment, if effective, will cause a paradigm shift in our understanding of sepsis and will help illuminate the mechanisms of the pathophysiologic derangements and improve our knowledge of the disease process.

## IX. MONITORING AND QUALITY ASSURANCE

### a. Independent monitoring of source data

- The PI will designate an Independent Data Safety Monitoring Board to perform an independent review of ongoing study progress and safety. The monitoring committee for this study will be comprised of personnel not associated with this research project and thus who work independently of the PI. They will be qualified to review the patient safety data generated by this study because of their clinical expertise in the area of sepsis.

### b. Safety monitoring (e.g., Data Safety Monitoring Board, etc.)

- Study progress and safety will be reviewed monthly (and more frequently if needed). Progress report including patient recruitment, retention/attrition, adverse events will be provided to the independent monitoring committee following each of the monthly reviews.

### c. Outcomes monitoring

- Preliminary statistics will be computed when we have enrolled 50% of the expected number of participants, if a significant difference ( $RR > 4$ ) in favor of the control group is found in terms of the primary endpoint, the study will be ended at that point.

### d. Adverse event reporting guidelines

- An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (lab test value, vital signs, electrocardiogram finding, etc) or any combination of these. A serious adverse event (SAE) is any AE that results in one or more of the following outcomes: death, a life-threatening event, prolongation of existing hospitalization, persistent significant disability/incapacity, or other important medical events based on appropriate medical judgement. SAEs will be evaluated and categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study.

intervention. Due to the nature of the illness severity of enrolled study subjects, SAEs are expected to be highly prevalent despite being unrelated to the study intervention. SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to independent monitors and the IRB.



## X REFERENCES

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## Appendix

### Effect of IV Vitamin C, Thiamine, and Steroids on mortality of Septic Shock

## RECORD of subject screening, consent and enrollment

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